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Genetics of Type 2 Diabetes

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Abstract

Purpose of review—To provide an overview of the genetics of type 2 diabetes in the context of recent progress in the understanding of the genetic architecture of the disease and its applicability to the pathogenesis of the disease as well as efforts to individualize therapy in type 2 diabetes. Efforts are underway to understand how these loci alter measurable physiologic processes in nondiabetic humans. However, it is important to understand the potential pitfalls in such studies and the limitations underlying measurement of insulin secretion and action using qualitative methodologies.

Recent findings—The availability of large population-based cohorts and the ease with which large numbers of common genetic variants can be genotyped has enabled the discovery of multiple loci and pathways associated with type 2 diabetes. Recent efforts examining quantitative traits such as fasting glucose concentrations have led to the discovery of other genes likely to be important in the development of diabetes.

Summary—The past 4 years have witnessed a significant increase in our understanding of genetic predisposition to type 2 diabetes. Hopefully more progress will be made in applying this knowledge to the pathophysiology of type 2 diabetes in the coming years.

Keywords

Type 2 diabetes; genetic predisposition; quantitative traits

Introduction

Type 2 diabetes is a complex and pleomorphic metabolic disorder arising from a complex interaction between genes and the environment. It is characterized by defects in insulin secretion and insulin action which lead to hyperglycemia [1]. Indeed hyperglycemia is used to define the presence or absence of the disease: - fasting hyperglycemia (>126 mg/dl), after an oral glucose tolerance challenge (120 min value > 200mg/dl) or if a random glucose >200mg/dl, on two or more occasions. However, it has long been recognized that people with impaired fasting glucose and or impaired glucose tolerance have characteristics similar to people with established type 2 diabetes. Moreover, the more significant the elevation in fasting or post-challenge glucose concentrations, the more likely is the transition to type 2 diabetes [2,3].

The concurrent availability of high-throughput genotyping techniques and large, multicenter case-control cohorts since 2006 has enabled the discovery of multiple common genetic variants associated with type 2 diabetes [4] or intermediate phenotypes such as glucose-insulin ratios in response to a standardized challenge [5].

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Conflict of Interest: None

The genetic architecture of type 2 diabetes

At the present time, knowledge of loci conferring risk of diabetes is limited to two extremes of a spectrum – extremely rare variants conferring disease risk in highly penetrant, autosomal dominant fashion or, conversely, common variants (minor allele frequency ≥ 10%) with weak to modest effects on disease predisposition (Odds Ratio 1.1–1.5). In some cases, variation in a single locus can fit both extremes of the spectrum. For example, variation in *WFS1* can cause the mendelian disorder of Wolfram Syndrome (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness - DIDMOAD) while other (much more) common variants are associated with type 2 diabetes [6]. The discovery of less common, more penetrant variants likely awaits the application of whole genome sequencing to large kindreds with a high prevalence of the disease.

In this sense the genetic architecture of type 2 diabetes differs significantly from that of type 1 disease where risk is also conferred by multiple loci. However, in the latter case, some loci have far more significant effect on disease e.g. rs3129934 in HLA class II (OR ~ 7) as well as, variants in *INS* and *PTPN22* (OR > 2). Other variants in loci such as *IL2RA* and *CTLA4* have effects on disease predisposition similar to those observed in type 2 diabetes [7]. The discovery of the association of *IL2RA* with type 1 diabetes served to illustrate some of the limitations of genetic association studies [8]. CD25, which is encoded by *IL2RA* is involved in immune regulation and is a phenotypic marker of T cells likely to regulate autoreactive clones; involvement in the pathogenesis of type 1 diabetes was not surprising. It also illustrated the sample size necessary to reliably detect association of relatively common variants with weak effect on disease predisposition [9]. Furthermore, the successful use of tag SNPs to detect a disease locus underpinned subsequent genome-wide association studies (GWAS) efforts. One final comment regards the statistical criteria necessary to accept an association as true – conventional correction for multiple testing is somewhat pointless - and depends on *a priori* knowledge of the prior odds against an association being true [10]. It is important to appreciate that some alternative measures to a pre-specified *P*-value for ranking signals in association studies may be susceptible to the minor allele frequency of the variants tested [11].

One significant advantage that genome-wide association studies (GWAS) have over candidate gene association studies is that they make no assumptions about disease pathogenesis. In contrast, candidate gene-based studies by definition assume that genes selected for study are important in disease pathogenesis, and therefore such studies are unlikely to discover novel mechanisms or pathways that lead to disease. This has indeed been the case with multiple loci associated with type 2 diabetes via GWAS which have unknown function or have been implicated in other disease states. Although the discovery of the association of *TCF7L2* with type 2 diabetes preceded the advent of GWAS, the methodology (and rationale) used was similar and similarly directed. Indeed prior to the discovery that genetic variation in *TCF7L2* is associated with type 2 diabetes other than the suggestion that it may regulate the differential processing of proglucagon, little was known about its function [12]. This is not to say that subsequent to its discovery, the body of knowledge regarding the function of *TCF7L2* has been consistent – a problem we will take up in the next section – however, it illustrates how undirected scientific inquiry can identify genes, pathways and processes not previously associated with a disease [13–16] (See Table 1 and 2).

Compared to a simple regression model incorporating blood pressure, triglycerides, HDL, glucose, body mass index and family history of diabetes, an identical model incorporating genetic information from 18 diabetes risk alleles had no predictive advantage for type 2 diabetes [17]. On an individual basis such data is of little use in predicting future risk of

diabetes. However, by implicating a biological pathway in the pathogenesis of diabetes, genetic association studies have provided a greater understanding of the pathophysiology of type 2 diabetes and identified potential new drug targets for the treatment of the disease. It may be important to emphasize at this point that magnitude of effect a locus has on disease development does not preclude significant therapeutic effects of compounds acting on these loci. For example, sulfonylureas (*KCNJ11*) and thiazolidinediones (*PPARG*) both have very significant effects on glycemic control although the common variants in these loci have weak associations with type 2 diabetes [4].

Initial GWAS studies used the presence of diabetes as a categorical trait (i.e. present or absent) and discovered several other loci associated with the disease (Table 1 and Table 2). In one case, *FTO*, the association with diabetes disappeared after correcting for BMI – the disease-associated variant predisposes to disease by increasing weight. Subsequently, analysis of quantitative traits such as fasting and 2-hour glucose concentrations has detected other loci that alter glucose homeostasis [5,18,19]. In the past year, *MTNR1B* which encodes the melatonin receptor 2, expressed in β-cells and has been recently shown to alter fasting glucose. It also increases the risk of type 2 diabetes [20] (Table 2 and 3).

Reduced birth weight is associated with risk of type 2 diabetes in several large studies. The HBCS study has suggested that the disease-associated variant in *HHEX-IDE* was also associated with low-birth weight. Conversely the opposite was noted with *CDKN2A/2B*. However, risk variants in some loci interacted with low birth weight to further increase the risk of diabetes development [21]. Subsequently, a larger cohort of mothers and their offspring suggested that *CDKAL1* and *HHEX-IDE* but not *CDKN2A/2B, IGF2BP2* and *SLC30A8* also affected birthweight [22]. More recently, in a smaller cohort (~ 5,500) of children of European ancestry (and in whom gestational age at birth was unknown) only *CDKAL1* was associated with birth-weight [23].

Effect of disease-associated variants on measurable physiology

One significant disadvantage of tag SNP methodology is that the subsequent elucidation of an etiological variant within the associated locus may not be straightforward. For example *IL2RA* is adjacent to *IL15RA* – another plausible candidate gene for type 1 diabetes – therefore a variant within the region may be associated with disease not because it is the true etiologic variant but because it is in linkage disequilibrium with it [8]. Similarly, the presence of a variant which causes a coding change in the gene product does not automatically qualify as the etiological variant. In such instances, fine-mapping of the locus is necessary to identify a variant (or variants) most associated with disease and with some measurable effect on physiology [24,25].

In type 2 diabetes some disease-associated variants have been associated with an intermediate phenotype such as insulin concentrations after a glucose challenge – a qualitative measure of insulin secretion – or with glucose/insulin ratios which have been used as a crude and imperfect measure of insulin action [26,27]. Indeed, subsequent to the discovery of the association of *TCF7L2* with diabetes [28] analysis of OGTT data suggested that the (T) allele of rs7903146 impaired insulin secretion [27,29,30]. However, fine mapping of the locus in several populations was required to demonstrate that if rs7903146 is not the causative variant for type 2 diabetes, it is indistinguishable from it [31].

Unfortunately, such qualitative measures of insulin secretion and action cannot account for the compartmental kinetics, the pulsatile nature of insulin secretion or hepatic insulin clearance [32]. Attempts to better characterize the effect of *TCF7L2* on insulin secretion and action using modelling has yielded contradictory results; for example, Elbein et al. reported an effect on insulin action alone [33].

Although it is reasonable to expect that a better measure of the phenotype (e.g.: insulin secretion) being tested will require smaller numbers than would be required with a cruder measure (e.g.: insulinogenic index). However, designing such studies *de novo* requires a considerable amount of resources due to the frequent sampling and multiple immunochemical assays necessary to accurately measure secretion and action. Moreover, the sample size necessary to adequately power such studies is not certain and dependent on the effect size of the locus being tested. Another significant limitation is that the genetic architecture of many of the loci associated with type 2 diabetes is not well known creating uncertainty in the optimal design of such experiments if the etiologic variant at a given locus is unknown.

Consequently, most of the available data correlating genotype data with a physiologic phenotype has arisen out of large cohorts where simple phenotyping with oral glucose tolerance tests was already available. Consequently it is important to remember the limitations of homeostasis model assessment and other qualitative measures of insulin secretion and action. Stancakova et al. studied 5,327 non-diabetic men and concluded that 8 SNPs affected insulin concentrations 30 minutes after oral glucose challenge. However, 3 SNPs, including the diabetes-associated variant of *KCNJ11* (a gene which affect β-cell function), were nominally associated with the Matsuda index – a correlate of insulin sensitivity. In addition, 4 diabetes-associated variants were associated with indices of proinsulin conversion to insulin [34]. Although proinsulin concentrations in the peripheral circulation are considered to be a marker of β-cell health, they do not necessarily reflect secretion as its half-life is much longer than that of insulin or indeed c-peptide [35].

Type 2 diabetes is characterized by impaired insulin secretion and action (defined as the ability of insulin to suppress glucose production and stimulate glucose uptake). In addition glucose effectiveness (the ability of glucose *per se* to stimulate its own uptake and suppress its own release) is also impaired. In the postprandial situation defective suppression of glucagon secretion as well as accelerated gastric emptying may also contribute to the postprandial hyperglycemia observed in diabetes. Arguably, none of these other phenotypes are adequately addressed by a glucose tolerance test [36].

This may be one reason why to date most of the loci associated with type 2 diabetes seem to affect insulin secretion but not insulin action. Anther potential explanation is the modification of insulin action by environmental factors (that lead to weight gain) which outweigh any potential genetic effects. It is also important to remember that insulin secretion declines in concert with insulin action in impaired fasting glucose and impaired glucose tolerance [2]. Furthermore interventions, which decrease insulin secretion, lead to a measurable decrease in hepatic insulin action [37]. Finally, insulin secretion, when measured, is best expressed as a function of the prevailing insulin action [38].

More recently, over-expression of the α2A-adrenergic receptor in mice was shown to decrease insulin secretion. Subsequently the same group of investigators demonstrated that in humans variation in *ADRA2A* altered insulin response to intravenous glucose and was associated with type 2 diabetes [39]. Other novel loci have also been shown to alter fasting glucose as well as glucose and insulin responses to a standardized glucose challenge [5,19].

Variants associated with differential response to therapy

From a physiologic point of view, monogenic disorders are helpful in illustrating the importance of specific gene products, and their associated pathways, to a given process e.g. glucose homeostasis. One such example is maturity onset diabetes of the young (MODY): mutations in the glucokinase gene (*GCK* - MODY 2) alter the set point at which insulin secretion occurs but insulin secretion and action are unimpaired in affected patients.

Similarly, common variants in *GCK* are also associated with alterations in fasting glucose concentrations. As progress is made in understanding the genetic architecture of diabetes, it may be possible to discern different pathophysiology within the heterogenous grouping of type 2 diabetes. In such situations, a given therapy may be more effective in one subgroup of patients than it is in another group of patients. At present there are some hints that this could be the case although the applicability to therapeutic selection in individual patients is uncertain. For example, in some subtypes of MODY, insulin secretagogues seem to be more effective than insulin sensitizers or insulin [40].

Unfortunately, as it applies to the therapy of common varieties of type 2 diabetes examples where common variation alters response to therapy are harder to come by. In part some of these limitations are due to the nature of the disease process; compliance with treatment and lifestyle are likely to affect response far more than common variation. Furthermore, deciding what endpoint to measure may be problematic when determining efficacy of a given therapy; while HbA_{1c} might be an obvious endpoint, the duration of study may not be long enough to allow meaningful changes in HbA_{1c} [41]. In a similar vein, a random glucose > 300mg/dL is an arbitrary marker of sulfonylurea failure [42].

As discussed above, consideration needs to be taken of the genetic architecture of the locus under study. It is often wrong to assume that the presence of a variant identified by genome-wide association to be associated with disease is the etiological variant or indeed the variant modulating drug response. A suggested approach would be one where a homogenous, well-characterized population is studied over a short (but physiologically meaningful) duration and a surrogate physiological variable (e.g.: insulin secretion) is utilized as a measure of response [43,44].

Similar approaches have been undertaken to demonstrate that variation in *TCF7L2* may alter response to infused GLP-1 [45] and that *OCT1* may alter response to oral metformin [46]. In the former study insulin secretion in response to hyperglycemia and GLP-1 was utilized as an endpoint while glucose excursion after an oral glucose tolerance test was used in the latter. However, a recent study examined the effect of 2 loss-of function polymorphisms in *OCT1* and concluded that the response to metformin was unaffected in 1,531 subjects with type 2 diabetes [47]. The same group of investigators has suggested that 2 variants causing loss-of-function of cytochrome p450 2C9 (which metabolizes sulfonylureas) improves the therapeutic response to sulfonylureas [48]. The Diabetes Prevention Program (DPP) has also shown that some disease-associated variants are associated with impaired response to metformin [49], however, such variants are likely of little value in predicted individual response to pharmacotherapy.

Conclusion

Common genetic variation is associated with type 2 diabetes and the discovery of loci that affect diabetes risk, response to oral glucose, incretin effect and fasting glucose concentrations will help understand the pathogenesis of the disease and identify new targets for drug development. However, it is important to understand the potential limitations of such knowledge and the difficulties in designing experiments to understand their role in glucose metabolism and their effect on drug response in humans.

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Table 1

Loci associated with type 2 diabetes.

Gene	Name	Function	Traits associated with the gene or risk allele(s) other than type 2 diabetes
ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif, 9	A member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protein family it may be important in proteoglycan cleavage in inflammation	
CDC123-CAMK1D	Cell division cycle 123 homolog (*S. cerevisiae*) and Calcium/calmodulin-dependent protein kinase 1D	CDC123 is a putative regulator of the cell-cycle while CAMK1D is a protein kinase that may be important in response to chemokines	
CDKAL1	CDK5 regulatory subunit associated protein 1-like 1	Function is uncertain; the protein product shares homology with CDK5 regulatory subunit–associated-protein-1, a neuronal protein that inhibits activation of Cyclin-dependent kinase-5	Insulin secretion Proinsulin conversion Birth weight Crohn's Disease
CDKN2A/2B	Cyclin-dependent kinase inhibitor 2A and 2B	Function as cell growth regulators that control cell cycle G1 progression by inhibiting cyclin-dependent kinases. Abnormalities observed in many malignancies e.g. melanoma	Insulin Secretion Vascular disease
FTO	Fat mass and obesity associated	Function unknown but does not seem to affect energy expenditure and may be more likely to affect caloric intake	Affects fat mass thereby indirectly predisposing to type 2 diabetes
HHEX	Hematopoietically expressed homeobox	Encodes a member of the homeobox family of transcription factors	Insulin secretion Proinsulin conversion Insulin Action
HNF1B	Hepatocyte nuclear factor-1β	The gene has been shown to function in nephron development, and regulates development of the embryonic pancreas	Renal Cysts MODY 5
IGF2BP2	IGF-2 mRNA binding protein 2	Regulates IGF-2 translation by binding to the 5′ UTR of IGF-2 mRNA	
JAZF1	Juxtaposed with another zinc finger gene 1	Encodes a nuclear protein with three zinc fingers; functions as a transcriptional repressor	Height Prostate Cancer SLE
KCNJ11	Potassium inwardly-rectifying channel, subfamily J, member 11	A potassium channel that is part of the sulfonylurea receptor complex and which regulates insulin secretion	Insulin secretion Neonatal diabetes * PHHI
KCNQ1	Potassium voltage-gated channel, KQT-like subfamily, member 1	Encodes a protein for a voltage-gated potassium channel required for repolarization	Long QT syndromes
NOTCH2	Notch homolog 2	Encodes a member of the Notch family characterized by an extracellular domain consisting of multiple epidermal growth factor-like repeats. functions as a receptor for membrane bound ligands, and may play a role in pancreatic development	
PPARG	Peroxisome proliferator-activated receptor γ	A member of the peroxisome proliferator-activated receptor family of nuclear receptors. The protein product is a regulator of adipocyte differentiation	

Gene	Name	Function	Traits associated with the gene or risk allele(s) other than type 2 diabetes
THADA	Thyroid adenoma associated	Expressed in thyroid adenomas – it seems to interact with PPARγ - at least in the pathogenesis of follicular adenomas	
TSPAN8-LGR5	Tetraspanin 8 and Leucine-rich repeat- containing G protein- coupled receptor 5	Tetraspanin 8 is a cell surface glycoprotein that like other members of the Tetraspanin family it complexes with integrins. They mediate signals that regulate development and growth. Lgr5 is a potential marker of intestinal stem cells and hair follicles in humans. It is a target of *Wnt* signaling.	Bipolar Disorder
WFS1	Wolfram syndrome 1 (wolframin)	The gene product is a transmembrane protein and is also located in the endoplasmic reticulum. It is expressed in the brain, heart and β-cells	Autosomal dominant deafness Wolfram Syndrome

* PHHI = persistent hyperinsulinemic hypoglycemia of infancy.

Table 2

Loci associated with type 2 diabetes and fasting glucose

Gene	Name	Function	Traits associated with the gene or risk allele(s) in addition to fasting glucose and type 2 diabetes
ADCY5	Adenylate cyclase 5	Formation of adenylate cyclase	
ADRA2A	Adrenergic alpha-2A receptor	This receptor is expressed in β-cells and modulates insulin release	Insulin Secretion
DGKB-TMEM195	Diacylglycerol kinase beta and Transmembrane protein 195	DGKB encodes an isotype of diacylglycerol kinase which increases diacylglycerol and therefore increases insulin secretion. TMEM195 is a membrane phosphoprotein	
GCK	Glucokinase	Three tissue-specific forms phosphorylate glucose to produce glucose-6-phosphate in the liver and the β-cell	
GCKR	Glucokinase regulator	A regulatory protein that inhibits glucokinase by non-covalent binding to form an inactive complex	
MTNR1B	Melatonin receptor 1B	Encodes one of two high affinity forms of a receptor for melatonin	Insulin secretion
PROX1	Prospero protein homeobox 1	This a corepressor of hepatocyte nuclear factor 4α which plays an important role in β-cell development	
SLC30A8	Solute carrier family 30 (zinc transporter), member 8	Expressed in β-cells – it is a Zinc transporter, this being necessary for insulin storage in secretory granules (an insulin hexamer with 2 Zn^{2+}) as well as being part of the secretory mechanism	Proinsulin conversion Insulin secretion
TCF7L2	Transcription factor 7-like 2	This gene encodes a high mobility group box-containing transcription factor that plays a key role in the *Wnt* signaling pathway	Proinsulin conversion Insulin secretion ?Insulin action

Table 3

Loci associated with fasting glucose.

Gene	Name	Function	Traits associated with the gene or risk allele(s) in addition to fasting glucose
C2CD4B	C2 calcium-dependent domain containing 4B	Encodes nuclear localized factor 2 which is expressed in endothelial cells but also in the endocrine and exocrine pancreas. It is upregulated by Interleukin-1β	
CRY2	Cryptochrome 2	This is an integral component of the system regulating the circadian rhythm in mammals.	Prostate Cancer
FADS1	Fatty acid desaturase 1	A member of the fatty acid desaturase gene family regulating the introduction of double bonds between defined carbons of the fatty acyl chain	Arachidonate concentrations
G6PC2	Glucose-6-phosphatase, catalytic, 2	An enzyme belonging to the glucose-6-phosphatase catalytic subunit family. It catalyzes the hydrolysis of glucose-6-phosphate, allowing the release of glucose (produced by gluconeogenesis or glycogenolysis) into the bloodstream	
GLIS3	GLIS family zinc finger 3	Encodes a nuclear protein with zinc finger domains and functions as both a repressor and activator of transcription. It is involved in the development of β-cells, the thyroid, liver and kidney.	Type 1 diabetes
MADD	Mitogen-activated protein kinase activating death domain	Part of the apoptotic signaling cascade triggered by tumor necrosis factor-α and activating MAP kinase	
SLC2A2	Solute carrier family 2 (facilitated glucose transporter), member 2	Encodes the GLUT2 transporter which carries glucose into β-cells and is therefore is part of the glucose-sensing of the β-cell.	* Fanconi-Bickel syndrome

* Fanconi-Bickel syndrome is characterized by proximal renal tubular dysfunction and glycogen accumulation in the liver and kidneys.